A Cross Sectional Study to Determine Prevalence of Insulin Resistance among HIV Positive Subjects on Anti Retroviral Therapy

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ABSTRACT

Introduction: The introduction of combination anti-retroviral therapy (c-ART) have declined the mortality and morbidity from HIV. However use of anti retroviral therapy have lead to metabolic disorders like impaired glucose tolerance and diabetes, as well as lipid disorders leading to an increase of cardiovascular disease. This study was aimed at to find out the prevalence of the insulin resistance and association of the insulin resistance with clinical and biological variables, including serum adipokines in HIV infected non-diabetic population undergoing combination ART therapy.

Material and Methods: A cross-sectional research was done in a cohort of HIV-1-positive patients attending Anti Retroviral Treatment Center (ART) of a tertiary care Hospital from December 2017 to December 2018. HIV-infected cases above 18 years, undergoing stable cART for at least 6 months were included in this study. The patients were asked to complete a questionnaire during the medical visit for demographic parameters and for personal and family medical histories. Investigations such as fasting plasma insulin, and circulating adiponectin, leptin, resistin, tumor necrosis factor alpha (TNF-alpha) and interleukin-6. (IL-6) levels were carried out.

Results: A total of 64 patients (aged 16–68 year, median: 31 years) including 40 men (62.5%) and 12 women (37.5%) were included in the study. Forty four patients (68.75%) were diagnosed with IR based on QUICKI values lower than the cut-off point. The presence of the IR was not influenced by either the time of the HIV diagnosis or by the duration of cART. Treatment with protease inhibitor therapy, decreased adiponectin and increased serum triglycerides were associated with increased IR.

Conclusion: We observed that the prevalence of the insulin resistance more in non-diabetic cases with HIV infection undergoing antiretroviral therapy and also there is an increased risk of developing diabetes mellitus and other cardiovascular diseases. Hence this study recommends that the management insulin resistance should be a integral component of HIV-infection therapeutic strategy.

Keywords: Insulin Resistance, Diabetes Mellitus, Non Communicable Diseases, Complications, HIV-AIDS, Anti-Retroviral Therapy

INTRODUCTION

Introduction of combination anti-retroviral therapy (c-ART) have declined the mortality and morbidity from HIV. However use of anti retroviral therapy have lead to metabolic disorders like impaired glucose tolerance and diabetes, as well as lipid disorders leading to an increase of cardiovascular disease. Data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) suggest that the risk of a myocardial infarction is more than doubled among HIV patients with Diabetes Mellitus (DM).[1] Various factors contribute to insulin resistance among HIV positive patients e.g. obesity, genetic influences, physical inactivity, antiretroviral drugs and lipodystrophy (which may be a consequence of treatment, particularly with thymidine analogues).

Globally the research suggests that the current antiretroviral regimen is associated with increased risk of glucose metabolism abnormalities. The negative effects of antiretroviral on glucose metabolism increases the risk of insulin resistance and diabetes in HIV-infected patients receiving antiretroviral treatment.

The aim of the study was to evaluate the prevalence of the insulin resistance and association of the insulin resistance with clinical and biological variables, including serum adipokines in HIV infected non-diabetic population undergoing combination ART therapy.

MATERIAL AND METHODS

A cross-sectional research was done in a cohort of HIV-1-positive patients attending Anti Retroviral Treatment Centre (ART) of a tertiary care Hospital from December 2017 to December 2018. In the present study 64 HIV-infected cases, aged above 18 years, undergoing stable cART for at least 6 months were enrolled. All the cases were included after obtaining their consent and after approval of institutional ethical committee.

The data was collected using a standard, semi-structured, pre-validated case record proforma, which included their clinical, social and family history. General and systeminc examination findings were also noted. Anthropometric measurements (weight, height, BMI) were also measured and recorded.[2] Blood samples were tested for: Adiponectin, Resistin, Leptin, Tumor necrosis factor alpha - TNF-alpha, Interleukin-6 (IL-6), CD4 T cells count, HIV viral load, fasting triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein

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(HDL) cholesterol and fasting plasma glucose, fasting insulin.

Quantitative Insulin Sensitivity Check Index (QUICKI) was used to diagnose insulin resistance.

1/(log(fasting insulin µU/mL) + log(fasting glucose mg/dL)³

In normal populations, mean QUICKI levels range from 0.37 to 0.39.[4] Consistent with previous studies, QUICKI values were dichotomized at the cut-off of 0.33, lower levels signifying IR.[5,6]

STATISTICAL ANALYSIS

The data was represented in the form of tables and graphs for frequency analysis and expressed as mean, and median for measuring their central tendencies. In skewed data, the results were represented as median. The singnificance between the differences in means between groups were analysed using independent-sample t-tests at 95% confidence interval. SPSS version 21 was used to analyse the data in this study. Mann–Whitney test for non parametric continuous variables, Chi-square or Fisher's exact test for categorical variables were used to test for statistical significance. Linear regression models were fitted to QUICKI score to test the association of IR with normally distributed continuous variables, included in the multivariate models either because of their known or suspected association with IR or based on an observed univariate association with QUICKI. Serum triglycerides.

RESULTS

A total of 64 patients (age 16– 68, median: 31 years) including 40 men (62.5 %, age range: 18–68 years, median: 32 years) and 24 women (37.5 % age range: 16–62 years, median: 21 years) were included in the study. The mean BMI was 23.8 (± 2.9) kg/m2. The median time from HIV diagnosis was 82.5 months and the median time on antiretroviral therapy was 76.5 months. Forty nine patients (76.56%) had a current Protease inhibitor-based cART regimen. Median serum levels of adiponectin, leptin, resistin, TNF alpha and IL-6 were 11.4 µg/mL, 1.5 ng/mL, 5.4 ng/mL, 10.5 pg/mL and 27.5 pg/mL, respectively. Fourty four patients (68.75%) were diagnosed with IR based on QUICKI values lower than the cut-off point. The overall prevalence of IR was 68.45%. The patients were divided into Group 1 (patients without IR) and Group 2 (patients with IR). Group 1patients had a mean QUICKI value of 0.35 (±0.02) vs. 0.29 (±0.02) in Group 2. The subject characteristics stratified by IR status are shown in Table 1. Significant differences were noted in total cholesterol, triglycerides and adiponectin serum levels between the two groups. The prevalence of IR was not significantly different between men and women. No significant differences were found between Group 1 and Group 2 in age, BMI, total time on cART or current protease inhibitor treatment.

DISCUSSION

When the human body requires insulin levels that exceed

Variables	Total patients	Patients without IR	Patients with IR	P Value
N	64	20 (31.25%)	44 (68.75%)	
Age (years)	31	21	33	0.12
Males	40	12	28	0.14
BMI (kg/m²)	23.8 ± 2.9	21.6 ± 3.1	24.4 ± 3.8	0.001
Fasting glucose (mg/dl)	86.8 ± 12.8	82.6 ± 9.6	88.2 ± 14.5	0.16
CD4 cells (cell/mm³)[a]	420	515	430	0.54
Time on anti retroviral therapy (months)[a]	76.5	86	75	0.26
Time from HIV diagnosis (months)[a]	82.5	94	79	0.39
Current protease inhibitor treatment	49	14	35	0.001
Total cholesterol (mg/dl)	191 ± 36.4	184 ± 31	198.8 ± 40.1	0.03*
HDL cholesterol (mg/dl)	44 ± 12.4	42.4 ± 19.5	43.3 ± 12.4	0.58
LDL cholesterol (mg/dl)	110.86 ± 34.4	108 ± 31.7	113 ± 35.5	0.45
Triglycerides (mg/dl)	168	152.4	183	0.02*
Dyslipidemia[b]	52	20	32	1.00
hypertriglyceridemia[c]	48	22	26	0.36
Adiponectin (ug/ml)[a]	11.4	14.5	10.2	0.00*
Leptin[a]	1.5	1.8	1.3	0.59
Resistin[a]	5.4	5.3	5.7	0.68
TNF alfa (pg/ml)[a]	10.5	12.1	9.8	0.78
IL-6 (pg/ml)[a]	27.1	26.5	26.4	0.58

Data are shown as mean ± SD or number (percent).
[a]Results presented as median.
[b]Dyslipidemia defined as elevation of one of the following: total cholesterol, LDL cholesterol, triglyceride serum concentrations or a decrease of HDL cholesterol.
[c]Hypertriglyceridemia defined as serum triglycerides ≥150 mg/dl.
[d]* p<0.05 Group 1 vs. Group 2.
p values based on t-test for equality of means or Mann–Whitney test for continuous variables, Chi-square or Fisher's exact test for categorical variables

Table-1: Characteristics of study patients by Insulin Resistance (IR)

normal concentrations for maintaining normal physiological values of glycaemia, it is labeled as Insulin resistance.[7] Insulin resistance is associated with the increase risk of developing diabetes and obesity and also cardiovascular risk.[8,9,10] In the pre-cART era several cross-sectional studies reported slightly increased or normal insulin sensitivity when compared to uninfected controls.[11] Various researches have found 20 to 50% prevalence of insulin resistance among in HIV-positive patients. We reported higher prevalcence insulin resistance as compared to previous studies.

In this study, we found a better correlation between QUICKI and glucose clamp index of insulin sensitivity. This is observed as gold standard method for the assessment of insulin resistance.[12] In the current study, the insulin resistance among HIV-positive young adult cases was not confounded by the time of diagnosis of HIV or to the duration of starting anti-retroviral regimen, suggesting the effect of anti-retroviral regimen on insulin resistance may not produce an additive or long-term response. This finding was supported by other studies.[13] Reduction of prevalence of insulin resistance should be considered equal importance, since it is associated with CVDs and diabetes mellitus, stroke and increased morbidity and mortality. Hence the management of insulin resistance should be an intergral part of management of HIV-patients undergoing retroviral therapy.

Subjects in the study were in the age group of 16 years to 71years with the median age of 31 years. There was no significant association between age group and insulin resistance among HIV patients. This observation was contrary to results obtained by Carlos Jerico et al where there was a significant association between age and metabolic syndrome.[14] There was significant association between BMR and insulin resistance. Similar findings were found in the various studies.[15] Duration of anti retroviral treatment didn't showed any association with insulin resistance.[16] In this study, there observed a significantly reduced risk of insulin sensitivity as compared with patients which were not on therapy, and protease inhibitors led to a significant rise in total levels of triglycerides and cholesterol, this finding is also backed by other studies.[17]

Adiponectin, which is a peroxisome proliferator-activated receptor gamma action mediator[18], may increase the responsiveness of insulin in adipocytes through increased expression of GLUT4 gene and increased GLUT4 recruitment through the plasma membrane.[19] Many researcxhes have concluded that the adipocyte differentiation was hampered directly by the anti-retroviral therapy, which leads to the decrease in serum adiponectin levels, hence it was associated with development of insulin resistance[20], which shows an inverse between adiponectin levels and insulin resistance. Deloumeaux et al. In their similar study, also an inverse correlation between adiponectin and insulin resistance.[21] Viganò et al also found similar results in a study conducted among a cohort of HIV-infected youths. Other studies also found similar inverse correlation between the two parameters.[22,23]

CONCLUSIONS

The present study concluded that there is a significantly higher prevalence of inslunin resistance seen in nondiabetic subjects with HIV infection undergoing antiretroviral therapy, that was independent of the time of the HIV diagnosis and anti retroviral therapy. Insulin resistance was seen in subjects on protease inhibitor therapy.

Therapy with protease inhibitors also associated with rise in total triglycerides and cholesterol levels among the cases. Reduced levels of serum adiponectin was associated with increased prevalence of insulin resistance in the current study, hence proving its inverse correlation. Further research should be conducted to study role of adipokines in the pathogenesis and exact mechanisms of developing insulin resistance.

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